Toxemia of Pregnancy with Vomiting.

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TOXEMIA OF PREGNANCY WITH VOMITING.

ITS TOXIC MANIFESTATIONS, ITS RELATION TO ECLAMPTIC TOXEMIA, ACUTE YELLOW ATROPHY AND EXPERIMENTAL NECROSIS OF THE LIVER.

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With the introduction of the principles of asepsis into obstetrics and the consequent lowering of the death rate from puerperal infection, the attention of the physician has been directed to the study and relief of those morbid manifestations, accompanying pregnancy and the puerperium, which cannot be shown to be due to a direct bacterial infection.

This has led to an increased knowledge of such diseases as eclampsia and hyperemesis gravidarum, mainly through clinical and post-mortem studies. A closer investigation of the symptoms and course of the disease and of the pathological lesions has shown that they have a common origin in a state of intoxication, always accompanied by functional incapacity of the liver. This is shown during life by the well-known manifestations of the autointoxication and by the excretion of products of faulty metabolism, such as leucin and tyrosin, known to be associated with liver insufficiency. Pathological studies have shown that the liver is itself the seat of grave changes which seriously interfere with the proper functional activity of the organ. These facts suggest the theory of an autointoxication due to hepatic insufficiency as the underlying factor in the causation of these morbid manifestations.

To this autointoxication or hepatotoxemia is given the name toxemia of pregnancy, and it is regarded by some obstetricians as the cause of many of the troubles of gestation. Thus, to this origin, is ascribed grave vomiting of pregnancy (hyperemesis gravidarum), puerperal neuritis, eclamptic toxemia and perhaps gestatory psychoses. In addition it is believed that many of the

minor disturbances of pregnancy, as gastric disorders, headache and certain skin lesions, may be referred to a similar source.

The following review of the literature on this subject may seem to be somewhat extensive, but is thought to be necessary. It is reviewed for the purpose of showing (1) the identity of the liver lesions of toxemia of pregnancy with vomiting and eclamptic toxemia.* and for the comparison of these lesions with those of experimental liver necrosis; (2) the frequency with which acute yellow atrophy occurs and (3) the presence of more marked toxic symptoms.

The similarity between the liver lesions of toxemia with vomiting and of eclamptic toxemia is suggestive. Stone, in a comprehensive and searching review, draws attention to this resemblance. He reports three cases of toxemia with vomiting with one death. Post-mortem examination showed acute yellow atrophy. His conclusions are as follows:

"Eclampsia is now generally recognized as a toxemia whose chief lesion is a degeneration and necrosis with multiple hemorrhages of the liver. The kidney changes, although forming an important part of its terminal features, are essentially secondary. All the older theories of eclampsia have been successfully applied to the condition which is described as hyperemesis gravidarum. We have also found under this latter clinical picture lesions which are identical with those occurring in acute yellow atrophy of the liver. At the same time we know but little in regard to the pathogenesis of this latter disease, except that in one-quarter of its cases it is associated with pregnancy, thus indicating that it is probably due to a toxemia. An analysis of its symptoms also shows it presents essentially the same clinical picture as eclampsia In other words, under the clinical titles of hyperemesis gravidarum, eclampsia and acute yellow atrophy of the liver, we have found enough to warrant a definite statement that they are one and the same disease."

In Stone's cases the vomiting began early in pregnancy, in two

* At present, there is tendency amongst some obstetricians to refer to all of the manifestations of toxemia of pregnancy as eclampsia. This I would deprecate. The term, eclampsia, as usually understood and generally used, refers to convulsions, either gestatory, intraspartam or puerperal. It would therefore seem preferable that the autotoxic state be designated according to the more prominent symptom, as (a) toxemia of pregnancy with vomiting, and (b) eclamptic toxemia (toxemia with convulsions. This division will be followed in this paper.

For further study of the identity of these conditions, I would refer the reader to Stone's article in American Gynecology, 1903, and Edgar's Theory and Practice of Obstetrics, 2d edition, New York, 1904.

it is described as "coffee ground vomiting." The latter was marked in the patient who died. Jaundice was not observed. One patient suffered from epigastric pain. The postmortem examination showed acute yellow atrophy of the liver. The description of the liver follows:

"Color—Light yellow consistency, easily pitted under finger pressure; cut surface smooth and of fatty appearance; lobules distinguishable; no congestion; vessels empty; both lobes showed uniform character; weight 36 ounces; gall-bladder contained bile; ducts pervious.

"Microscopic.—The cells of the greater part of each lobule have undergone fatty degeneration. Around the periphery of the lobule is a fringe of cells which are in a state of coagulation necrosis. The periphery of the lobules is further characterized by marked congestion of the capillaries issuing from the portal (interlobular) veins. This injection can be seen in the stained specimen with the naked eye. In the interlobular tissues there are blood vessels into which has occurred an immigration of leucocytes. The sublobular veins are empty." Thus he finds under the clinical picture of hyperemesis a lesion corresponding to acute yellow atrophy of the liver.

But this is not a new theory. Roughton, in 1885, suggested the probability of a common cause of persistent vomiting and eclamptic toxemia. He reports a case of a primipara, aged 20, who began to vomit in the sixth week of pregnancy. This continued with increasing severity until four and one-half months, when it became continuous. Emaciation ensued and the eyes were sunken and surrounded by black halos. Jaundice was present and the urine contained albumen and casts. With the onset of delirium labor was induced. Bile stained liquor amnii was found. The patient had post-partum hemorrhage, but recovered after a slow convalescence. In this case there was, I think, sufficient clinical data to make a diagnosis of acute yellow atrophy.

Gueniot from a study of collected cases divides vomiting of pregnancy into simple and grave, or irrepressible. He reports 118 cases with 46 (38.9 per cent.) deaths as follows:

RECOVERIES—SEVERE CASES.

Without abortion	31
With spontaneous abortion	20
With induced abortion	21

DEATHS.

With abortion	28
After spontaneous abortion	7
After induced abortion	11

These results occurred under all forms of treatment from copious draughts of wine to the application of leeches to the cervix.

Graefe ascribes the irrepressible vomiting of pregnancy to hysteria in many cases and thinks that suggestion and isolation of the patient are important in treatment. He reports one case cured by reposition of the uterus and the administration of purgatives and tonics.

Zabonisky's experience has led him to believe that the vomiting in many cases is due to a reflex neurosis and that the interruption of pregnancy is not always curative. He reports three cases, two primiparæ and a multipara, all of which terminated fatally. The postmortem examination disclosed a cancer of the stomach in one, pulmonary tuberculosis with fatty degeneration of the liver and kidney in the second, and in the third acute yellow atrophy. In the first, vomiting began at the eighth month; in the second, about the first month and ceased by the fifth; in the third, jaundice was present and albumen appeared in the urine.

Baisch does not accept unreservedly either of these theories. He regards hyperemesis as a reflex phenomenon, affecting either the motor or secretory function of the stomach, due to an irritation preceding from the periphery and transmitted tc the vomiting center. The uterus, the nerve centers in the medulla or the stomach itself may be points where the exaggeration of the reflex occurs and, consequently, treatment should be directed to meet each individual case. In his experience the cases of the gravest prognosis were accompanied by abnormal salivation. The relation between the villi and the uterine wall is said to be the probable primal cause of the disturbance. He summarizes twenty-two theories in regard to causation, grouped under the four headings of (1) definite organic lesions, (2) autointoxications, (3) reflex neuroses and (4) bacterial infection. He reports two cases in which pregnancy was interrupted with a favorable outcome.

Beatty reports a case of vomiting at the second month, accompanied by jaundice and colorless feces. There was delirium before death and the autopsy showed acute yellow atrophy. He also

collected fourteen cases of acute yellow atrophy from the American literature.

McPhedran and MacCallum report a case of grave vomiting, at four months of pregnancy, in a primipara, aged 24. The onset followed an attack of influenza from exposure. Epistaxis was noted, also jaundice and clay-colored stools. Hebetude persisted for five days, passing into coma with muttering. Vomitus was dark and grumous. Bile and leucin and tyrosin crystals were present in the urine, microscopically. Postmortem examination showed acute yellow atrophy of the liver, confirmed by histological examination. Liver was 25 ounces in weight, flaccid rather than friable, and red with yellow patches. The hepatic parenchyma was best preserved immediately beneath the capsule. The first change from the normal was manifested by coarse granulation or fatty vacuolation. The enlargement of the bile capillaries is another feature of the change. In cells which are coarsely granular but from which fat is absent, the membrane only of the nucleus may be detected, all else having vanished. In the enlarged cells, in which the fatty degeneration alone is prominent, the fat is collected in large droplets, separated from each other by protoplasmic septa in which the granules are collected. Examples of cell division are sufficiently abundant to warrant the conclusion that while there is atrophy in one part, there is regeneration in another. It might be thus possible to explain cases of recovery from acute yellow atrophy. They conclude that the destruction of the liver cells points to the presence of a poisonous element as the cause of the disease.

Another case which is reported by Snell with postmortem, is interesting from the similarity of clinical course to the one reported here and also from the histological description. Vomiting occurred in a primipara, aged 20, at three and one-half months of pregnancy; it continued with increasing severity until five months. The vomitus was at first blood stained and later "coffee ground." Slight jaundice was present in the fifth month, and there was wandering delirium and much emaciation. Death occurred seven days after the jaundice first appeared. Necropsy examination showed a dark red liver mottled with yellow. Histologically, the different parts showed varying amounts of connective tissue. Where the change was most advanced, there were large tracts in which the liver substance was represented only by a few islands of hepatic tissue, many of which contain a few droplets of fat. Granular masses of pigment were also seen. Numerous branching ducts

lined with cubical epithelium were present; where the process was most advanced, the liver lobules were large. The center of the lobule was occupied by a loose reticulum of connective tissue in which a few liver cells undergoing fatty degeneration were enclosed. The connective tissue everywhere took the form of a loose mesh work with oval or spindle-shaped nuclei. The degeneration of the liver cells was seen only where the connective tissue was formed. He concludes that the primary process was an acute formation of connective tissue, the destruction of the liver substance being secondary.

Rudisch and Strauss report two cases of acute yellow atrophy, one a primipara, aged 21, was four and one-half months pregnant. The history was of two weeks' headache, vomiting and epigastric pain. Epistaxis, jaundice and albuminuria were present with hyperesthesia and subconjunctival hemorrhages. Stupor, with increasing icterus, was followed by death. At necropsy the liver was found to be soft, fatty, with ochre-yellow areas surrounded by a red rim. Microscopically, there was granular degeneration and towards the center of the lobule the cells became more and more changed. There were a few leucocytes and no regeneration. They suggest coagulation necrosis rather than fatty degeneration.

Behm claims that the source of the poison is to be sought in the degeneration of the placental cells, and explains its frequency in the early months by the fact that at this time the active degenerative changes occur. He divided the cases as to etiology into five groups: (1) Diseases of organs; (2) reflexes from pelvis; (3) infections; (4) intestinal autointoxication; (5) retained placental tissue following abortion. He notes illustrative cases; in one the placenta was retained several days after abortion and vomiting persisted until its removal.

Charpentier de Ribes and Bouffe de St. Blaise report a case of a primipara in the sixth month of pregnancy, who was taken with severe vomiting which became more or less persistent. In three weeks she was delivered spontaneously and vomiting stopped; but delirium grew worse, passing into convulsions, and death occurred seventeen days after labor. The urine contained a large quantity of albumen. Autopsy revealed hemorrhagic areas in liver, an old infarct and many subcapsular hemorrhages. The complete analogy between this lesion and that of eclampsia is noted and it is considered sufficient proof of the hepatic origin of the vomiting.

Bassoe and Wells report three cases of acute yellow atrophy of the liver, one, a primipara, aged 20, became sick in the sixth month of pregnancy with headache, slight jaundice; no mention is made of vomiting. A few days later she developed some fever and became comatose. Urine showed bile, leucin, tryosin, albumin and casts. Coma continued for eighteen hours without convulsions or delirium, terminating in death. At necropsy, the anatomic diagnosis was as follows: Puerperal state, general jaundice, acute yellow atrophy of the liver, multiple hemorrhagic extravasation (subpleural, subpericardial, periaortic, subcutaneous and pulmonary). Enlarged thyroid and hypophyses. Acute degeneration of kidneys, moderate right hydronephrosis.

The liver appeared much smaller than normal when *in situ*, weight was 1,020 grammes. Surface was smooth, presenting red and yellow areas. Cut surface was mottled, brownish red and yellow. Microscopically, in a section through an area more normal than the rest of the organ, there were areas of necrosis both central and peripheral which showed remains of destroyed liver cell nuclei lying in the original stroma which was unaffected. In a section through a yellow area, the lobules were indistinct and smaller, individual cells appearing as swollen yellow granular necrotic plaques with indistinct outlines, showing no nuclei. A section through the red area showed more marked changes with proliferating and new formed bile ducts. The kidney showed cloudy swelling. They draw attention to the theory of autolysis, first suggested by Flexner, and remark that the changes may be due to this. Correlating the processes of autolysis and acute yellow atrophy, they first sum up the usual changes, a marked necrosis of the liver, involving all the cells of the lobules in large areas, sparing other areas and also sparing the connective tissue of the lobules that are involved, the blood vessels and interlobular ducts. In many cases greater or less degrees of regeneration have been observed. This is found to consist of a general proliferation of the surrounding cells, both of connective tissue and of bile-duct epithelium. The former multiplies and leads to a large excess of connective tissue, which would undoubtedly prevent the liver from ever becoming normal again. "It would seem, therefore, that we are dealing with an intoxication by a substance with a considerable degree of specificity for certain cells, those of the hepatic cords, which spares ever so closely related cells as those of the bilt ducts." They also refer to the lack of fat or of fatty degeneration as shown by osmic acid staining.

Opie, in a contribution to the pathology of necrosis of the liver, reports a case of a primipara, aged 28, in the second month of pregnancy, who complained of nausea and vomiting, which became so persistent that rectal feeding was necessary. Vomiting continued and became blood stained. The uterus was emptied after twenty-five days' treatment. Vomiting ceased but death occurred three days later, after torpor and coma. There was no jaundice. Necropsy examination showed the liver to be of small size, 1,000 grammes, soft and, on section, of a bright yellow color. Microscopic examination showed that the central part of each lobule had undergone necrosis, leaving intact a narrow peripheral zone. Immediately about the central vein of each lobule, nuclei of the endothelial cells and rarely nuclei of the hepatic cells were preserved, but elsewhere both had disappeared. In the peripheral part of the necrotic area occupying a zone in width about one-fifth of the radius of the lobule, parenchymatous cells were broken into particles and had lost their columnar arrangement. In the central part of the lobule, necrotic cells were vacuolated, as if the seat of fatty degeneration. In the peripheral zone, nucleated hepatic cells in contact with the necrotic tissue had undergone advanced fatty degeneration. Opie designates this condition midzonal necrosis and likens it to Stone's case. He considers the association of midzonal necrosis and advanced fatty degeneration to be due to the fact that the cells least injured undergo fatty degeneration. Of nine cases of midzonal necrosis, it occurred three times associated with pregnancy, and, of these, two had puerperal infection. Reference is also made to four cases of peripheral necrosis of the liver, all of which occurred in association with pregnancy. Three cases of eclamptic toxemia preserved characteristic lesions. The liver was studded with hemorrhagic foci, varying in size, in such areas, the liver cells had undergone necrosis and lost their nuclei. The body of the cell, losing its definite outline, was merged with the dense network of fibrin, which made its appearance throughout the necrotic tissue; abundant hemorrhage had occurred in and about the necrotic tissue. The smallest necrotic areas were always in contact with the portal spaces. The fourth case, a Cesarean section with general peritonitis, showed similar lesions in a more marked degree. Opie states that midzonal necrosis or combined middle and central zonal necrosis is probably an early stage which has its termination in acute yellow atrophy, and that the liver is enlarged rather than atrophied.

There has been so far considered only the results of the toxic

process in so far as it affects the liver. There is no doubt that grave changes do occur in the kidney and other organs, as evidenced by hemoglobinuria, albuminuria and casts; but they are of secondary importance. Stone in referring to the proof of the greater importance of liver lesions states that eclampsia without albuminuria occurs in one-tenth of all cases, and that albuminuria may be one of the last signs. I consider, however, that this is simply a question of the stage and grade of the disease; if cases are seen at the onset of toxic symptoms the albuminuria is often absent and, in fulminating cases, death occurs without marked kidney change. The frequency of albuminuria is to be considered; in pregnancy, it is the rule rather than the exception, as shown by Little's statistics. These statistics bear out a study of my own, made at the Lying-in Hospital, in which albumin was present in varying amounts in about 90 per cent. of all primiparæ at or about labor. Meyer-Wirz, in a clinical study of 117 cases of eclamptic toxemia, reports that in 38 who were under observation before the onset of the disease, eight showed complete absence of albuminuria before the first convulsion; also that in the 35 cases, which came to autopsy, eight were shown to be free from renal affections. No doubt as the disease progresses there cannot but be grave changes in the kidneys, *i.e.* fatty degeneration, cloudy swelling, acute nephritis, etc.

Bar, in analyses of the microscopic findings in twenty-four eclamptic subjects, does not remember a single instance in which gross pathologic lesions were not seen. In twenty-four cases, the kidneys were profoundly affected in four, the lesions were moderate in nine, and in eight they were of slight intensity. The liver was affected in most cases, but not proportionately to the intensity of the kidney lesions. Some of the mildest kidney lesions were accompanied by the severest liver lesions. He concludes that the disease is due to the action of some powerful poison, which may affect the kidneys in some cases and the liver in others.

The symptoms of eclamptic toxemia, with the accessibility of the urine for examination, naturally led to the conclusion that the disease was due to an acute inflammation of the kidneys. However, areas of necrosis are found so constantly in the liver that they are a characteristic of the condition.

Neuritis is among other evidences of toxic disturbance in pregnancy. Of this interesting condition, Eulenberg reports four cases, complicating vomiting of pregnancy, with a collection of thirty-eight other cases of puerperal neuritis. He divides the

affection into two groups, basing the distinction between them simply on the extent and severity of the lesions presented, and so divides them into (*a*) the less severe and localized forms and (b) severe diffuse forms which may simulate Landry's paralysis or involve the cerebral nerve areas. He concludes that they usually arise from autointoxication.

Nicholson divides the etiological classification as follows: (1) Those cases arising from a toxemia; (2) those cases arising from a septic process; (3) those cases resulting from some mechanical agent during labor or in the early puerperium. He reports two cases, in one of which there is a vague history of a mild toxemia in the early months; the other followed a difficult forceps labor with unrepaired complete laceration of the perineum seen two months after childbed. He states that the improvement in severe conditions is slow.

Landemann also reports a case of pregnancy with polyneuritis. Necropsy examination showed cloudy swelling and fatty degeneration of the liver without necrosis of cells. The spleen and kidney showed coagulation necrosis, which he considers to be an evidence of the toxic cause of the disease.

The writer would add the following case of toxemia of pregnancy with vomiting, jaundice and neuritis.

Primipara, aged 36; married.

Previous History.—Patient was never a strong child and had diseases of childhood. No history of acute rheumatism, but has had scarlet fever. Has had "heart disease" attributed to lifting a heavy weight.

History of Present Illness.—Patient had been married five months. Menstruation was present once after marriage. When two months pregnant vomiting began in the mornings, persisting with intervals of relief. At three months, vomiting was so persistent as to confine the patient to bed. She, however, looked upon this as the usual course and refused to call a physician. At four months, vomiting was so severe and continuous that a physician was consulted. He treated the patient with rectal feeding, cocaine by the mouth, and after several days curetted her in bed, in the Sims position and without anesthesia. Eight days after this curettage the writer was called to take the case owing to the departure from town of the first physician, who assured me that the uterus had been thoroughly curetted. The vomiting, at that time, was persistent and continuous, and there had been no retention of food for three days. Vomitus was dark and blood-

stained. Face was drawn, tense and anxious, with prominent eyes and photophobia; the patient was restless and querulous. The odor of acetone from the breath was distinctly evident on entering the room. There was slight jaundice. There was a marked limitation of field of vision. Patient complained of pain in the epigastrium and in the region of the lower part of the esophagus. Temperature was 99° and pulse 140, thready and of extremely high tension. Heart was slightly enlarged and showed a mitral stenosis; lungs were negative. Abdomen was flaccid and no pain nor tenderness was appreciable on palpation; no enlargement of the liver could be made out and no tenderness on pressure could be elicited.

Vaginal examination revealed a soft, congested vagina and soft cervix, which was firmly closed. Uterus was soft, about the size of a two-months pregnancy, markedly retroverted, but mobile and capable of replacement. Appendages were free and negative and no vaginal discharge was present.

Urine was scant, of high specific gravity and showed a large amount of albumin, one-fifth by bulk, with granular and hyaline casts in very large numbers. Leucin and tyrosin were also present microscopically.

The treatment begun at this time consisted of large rectal salines as often as they could be retained, predigested food by the bowel in the form of peptonized milk, predigested beef, etc. Chloretone, grs. v, was given every four hours to control irritability of the stomach and restlessness of the patient.

Patient improved slowly during the first week and, at the end of that time, vomiting was only occasional. Easily digested food, as light cereals, broth, etc., were well taken. Celestin Vichy was retained often to the amount of two liters daily. As the irritability of the stomach improved small doses of extract of ergot and strychnia were given with the aim of aiding involution of the uterus. This involution, however, did not progress.

The urine increased in amount and albumen lessened, although granular casts were still present. The jaundice still persisted. There was no vaginal discharge; pain was less and still referred to the epigastrium. Temperature was 98°-99° and pulse was 108-120.

This condition continued until five weeks after the first curettage. Vomiting still continued in a mild form, although it was absent once for two days. Jaundice disappeared at the end of the third week. Nutrition improved. An annoying complication, an

infection of the gums, caused an abscess to form at the roots of two teeth and necessitated extraction to favor drainage. An abscess also formed in the submaxillary space from breaking down of an infected gland. The temperature during this time varied from 98°-100°, and was thought to be accounted for by the suppurative condition of the jaw and a mild bronchitis which began during the fourth week after the first curettage. Pulse ran from 104-120 with good tension.

The medication at this time consisted of fluid extract of digitalis with chloretone and trional at intervals for sleeplessness and pain. Ergot was discontinued in the second week after first operation.

Daily examination of the urine showed an occasional trace of albumin and an occasional hyaline cast. Small saline enemata and copious draughts of vichy were given. The condition of the uterus remained unchanged, soft, about the size of a two-months pregnancy, with cervix tightly closed. No vaginal discharge was evident and a vaginal douche was given every other day to promote involution. The possibility of retention of products of impregnation was considered; but, in view of the absence of pelvic or uterine symptoms, the patient's precarious condition and the assertion of the operator in regard to completeness of the curettage, a secondary operation was not done. In the sixth week after the first curettage, pain appeared in the legs. This was referred to the extensor muscles of the thigh and later involved the flexors of both thighs and legs with considerable wasting and marked hyperesthesia. Flexion and extension of the toes was imperfect, and stimulation on the sole of the foot caused a movement of the leg, but none of the toes. Nerve points of leg were sensitive to pressure. From severity of the pain and loss of power, with the reaction of degeneration, a diagnosis of neuritis was made. During this time there were marked mental symptoms, *e.g.* wandering, loss of memory, inability to recognize friends and hysterical manifestations. These were so marked that the possibility of Korsakoff's psychosis was considered.

At the end of the sixth week, while vomiting was still occasional, the temperature which had previously been 100° or lower, began daily to take on a progressive rise, arriving finally at 104°, pulse 120.

At this time there was a slight discharge, and vaginal examination found the cervix to admit one finger. The examining finger was able to feel placental masses. Curettage was done with tem-

perature 104°, pulse 140, six and one-half weeks after the first curettage.

Ether was given, in spite of the bronchitis, as the heart condition was such as to make chloroform inadvisable. The cervix was found to admit one finger and was easily dilated instrumentally. At the fundus was found a placental mass intact, as large as an orange measuring 4 x 5 x 3 cm. This mass was firm and odorless. There was slight softening over an area as large as a quarter in one corner. The remnants of the membranes could be made out and the remains of the cord 3 cm. long. Uterus was gently scraped with a large curette and placental forceps, and packed with gauze which was removed on the following day. Hypodermoclysis was given under the breasts and repeated in 24 hours. The patient's condition was most precarious for the first three days, involuntary defecation being present. Pulse ran from 130-150, requiring constant stimulation with digitalis, strychnia, adrenalin and camphorated oil hypodermically.

Temperature was normal on the third day and convalescence was slow, interrupted by the sinus in the jaw requiring further drainage. The neuritis did not improve and the loss of power was marked. At the present time, twelve months after the curettage, the patient has not entirely recovered complete power in her legs. The pelvic examination, two weeks after operation, showed a well-involuted uterus with healthy appendages, but again retroverted. Careful inquiry laid bare the fact that the fetus had escaped, the day following the first curettage, while the patient was being given an enema.

Diagnosis.—Toxemia of pregnancy with vomiting. Acute yellow atrophy of the liver. Mitral stenosis. Mild bronchitis. Puerperal neuritis. Retained secundines.

This case is chiefly of interest from the fact of its similarity in clinical history to cases reviewed in this paper (vide supra) in which the post-mortem reports showed acute yellow atrophy. There is throughout these reports a singular similarity in clinical reports in those cases which had been curetted or had labor induced. In cases without marked toxic symptoms, vomiting ceased as soon as the products of conception, including the placenta, had been removed: although death may have occurred later. Behm's case in which the placenta was retained, vomited until its removal. The case reported here, although the symptoms were alleviated by flushing the organs through the stomach and rectum, vomited more or less until removal of the placenta, six and one-half weeks after

the escape of the fetus. In this connection Hitschmann reports a case in which eclampsia occurred in a four and one-half months' pregnancy as the result of a mole.

Gueniot's figures show conclusively that termination of pregnancy has a direct effect upon the mortality. In cases without abortion, the mortality was 90.2 per cent.; with spontaneous abortion, 35 per cent., and with induced abortion, 52.3 per cent. Hirst in 239 cases, gives a mortality of 30.7 per cent. in all. In cases treated by abortion the mortality was 25 per cent.; without abortion, 49.1 per cent. Thus, it will be seen that toxemia or pregnancy with vomiting is a disease which has a mortality even higher than that of eclamptic toxemia, of which we may take Meyer-Wirz' figures (27.3 per cent.) as a very fair estimate.

The question of anesthesia is an important one both in toxemia with vomiting and eclamptic toxemia, should it be necessary for operative interference or the control of convulsions, in view of the fact that Ballin has collected nine postoperative cases of acute yellow atrophy of the liver following chloroform narcosis. Vonderbrugge also reports a case of death in a child, 10 years old, with icterus and vomiting. Autopsy showed fatty degeneration of heart, liver and kidney. So, it would seem that in these conditions, it would be better to abstain from adding fuel to the fire and substitute ether for chloroform as much as possible.

In the review of these cases one is struck with the very large percentage of primiparæ, and the fact that the disease is at its height from three to four and one-half months.

Coffee ground vomit, due to disorganized blood, is shown to be a serious symptom in these cases. Esophageal pain is frequent. The combination of the two as an increasing amount of albumin in the urine should be indication for the serious consideration of operative intervention.

DO EXPERIMENTAL LIVER NECROSES AID IN EXPLAINING THE LIVER LESIONS OF TOXEMIA OF PREGNANCY?

Of the three theories of eclamptic toxemia based upon a biochemical foundation, the first is that of Viet, which assumes that the excessive influx of placental elements into the maternal circulation leads to the production of a cytolysin which is responsible for the morbid symptoms.

Ascoli supposes that the pathogenic changes and symptoms are due to this lytic substance—"syncytiolysin"—which is produced

in excess of the amount needed to counteract the invasion by the fetal elements.

Weichardt's theory is based on the supposition that, in the dissolution of the wandering placental elements, an albuminous material is formed, a "syncytiotoxin" which is poisonous to the mother. In normal pregnancies this poison is immediately neutralized by an adequate amount of antitoxin; but in cases in which the formation of this antitoxin is absent or deficient, the poison prevails and gives rise to eclamptic toxemia.

The results of Leiptman and of Wormser and Lathardt who repeated these experiments, do not support these theories. These writers did not obtain the "syncytiolysis in vitro" described by Viet, Scholer, Weichardt and Opitz. Neither were they able to induce eclampsia in rabbits as Weichardt claims to have done by the direct introduction of placenta cells into the vein. Also, the results of subdural injections failed to confirm Ascoli's views.

Dienst, in a recent article on the causation of eclamptic toxemia, ascribes great importance to the action of the mother's blood serum upon the red blood corpuscles of the child. He obtained blood both from the umbilical stump and from the placental end of the cord at the time of labor, and determined the action of these *in vitro*. He also tested the permeability of the expelled placenta by the injection of milk and of the placenta *in situ* by injecting methylene blue at low pressure.

In all 118 women were examined. The maternal blood serum, in twenty-four cases, agglutinated and eventually dissolved the red blood corpuscles of the respective children. Of these twenty-four cases, fifteen had impervious placenta, a normal course and no albuminuria. Of the other nine, with pervious placenta, seven were eclamptic and two had albuminuria. He, therefore, reaches the conclusion that, to this agglutination and hemolysis, is due the condition of eclamptic toxemia, and that this can occur only when there is a free communication between mother and child. Albuminuria occurs when the interchange is slight. He considers this action analogous to that of heterolytic sera; for example, he has seen in the liver of a rabbit after intravenous injection of human or dog's blood, changes similar to those caused by eclampsia. He states that there is not only a similarity, but an exact agreement between the clinical symptoms and the pathological lesions in both these conditions (eclampsia and transfusion with heterolytic sera). The hemoglobinuria is more marked in the experimental lesion.

In the study of experimental necroses of the liver, Pearce has shown that these lesions may be produced by the intravenous injection of hemagglutinins. The hemagglutinative sera were prepared by injecting the rabbit with various organs and fluids of the dog. The sera from these animals were then injected into the veins of the dog. These sera possessed the power of agglutinating the red blood corpuscles of the dog *in vitro*. The more powerful sera produced multiple liver necroses in dose of 1/1000 to 1/500 and in larger doses produced death in a few hours. The necroses developed in from 12 to 24 hours. They were usually widespread, closely massed and confluent. The surface of the liver presented a mottled appearance; small irregular yellowish brown or grayish yellow non-elevated areas, being sharply outlined by the deeply congested normal substance of the liver. Fine points of hemorrhage could be seen. The distribution of the lesions was superficial. All sera produce uniformly the same type of lesion, though not always the same degree of destruction.

Microscopically, the necrotic lesion involves the greater portion of a lobule, often the adjoining portions of several lobules. Frequently the necrosis is in the peripheral portion of a lobule, but, occasionally, the central and middle zones are involved; the altered area is frequently entirely surrounding the portal vessels. The necrosis is hyaline in character. Hyaline or conglutinative thrombi were found in the smaller portal veins and in the capillaries. It was possible, in serial sections, to demonstrate a relation between these thrombi and the necroses. The anatomic relation of the agglutinated red blood corpuscles to the lesion, in the absence of bacteria, phagocytic cell or fibrin thrombi, indicates that the necrosis is due to this obstruction of the smaller veins. Capillary thrombi may also occur in other organs, especially in the glomeruli of the kidney, periphery of the lung and in the adrenal with or without hemorrhage. Their occurrence, however, is infrequent in these places and is unaccompanied by necrosis. The greater frequency of necrosis in the liver is supposed to be due to the slow circulation and narrow capillaries of this organ.

Flexner, who has described these thrombi in various lesions in man, speaks of the alteration in form, cohesion and staining properties of the red blood corpuscles. Every transition was found from normal red corpuscles to the main agglutinative mass, in which the corpuscular outline was lost and a higher degree of refraction occurred. He found these thrombi in several of the

infectious diseases and in a *liver of eclampsia* in which the peculiar lesions (necrosis and hemorrhage) were abundant. The thrombi occurred in the neighborhood of areas of necrosis and hemorrhage.

The similarity of these experimental liver lesions to those of toxemia of pregnancy with vomiting and eclamptic toxemia, as described in the review of these conditions, is evident. The severity and extent of the experimental lesions depends upon the amount of the dose. Varying degrees of liver necrosis occur in toxemia of pregnancy as may be seen by reference to the lesions described by Opie and others. The periphery of the lobule is the seat of changes in experimental necrosis with moderate doses, while, with large doses, the middle and central portions are also attacked.

From the preceding review, it is evident that hemagglutinins, by the production of agglutinative red blood corpuscle thrombi, may cause experimental liver necroses. That the same mechanism holds for the liver lesions of eclamptic toxemia cannot readily be proven. The observations of Viet and others, however, concerning the presence of hemagglutinins in the mother's blood are suggestive. Moreover, in several eclamptic livers, which I have examined, these hyaline emboli, as described by Flexner, are to be found in direct relation to the necrotic areas.

There is evidence, therefore, that, in the toxemia of pregnancy, an agglutinative substance occurs in the blood and that this, by causing the clumping of red cells, leads to the occurrence of liver necrosis. It is possible that there may be, in addition, hemolytic and other toxic substances.

Dienst's experiments have added an additional argument in favor of this hypothesis by obtaining the hemagglutinin reaction *in vitro*, from the blood of eclamptics. His supposition that this hemagglutinin is formed in the fetus is weakened by Hitschmann's case of eclamptic toxemia, occurring in connection with a four and one-half months' hydatiform mole, and by Behm's case and the case here reported, in both of which symptoms of toxemia persisted after the expulsion of the fetus and until the removal of the placental remains. However, there is no proof at present that such a hemagglutinin is produced by the placental cells.

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